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Patentanmeldung Nr. Patent application No. Demande de brevet n°

04380158.8

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Triazole derivative PPAR modulators

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The original title of the application in the Spanish language reads as follows : Moduladores
de PPAR derivados de triazol.

TRIAZOLE DERIVATIVE PPAR MODULATORS

BACKGROUND OF THE INVENTION

5

Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor superfamily, a large and diverse group of proteins that mediate ligand-dependent transcriptional activation and repression. Three subtypes of PPARs have been isolated: PPAR α , PPAR γ and PPAR δ .

The expression profile of each isoform differs significantly from the others, whereby PPAR α is expressed primarily, but not exclusively in liver; PPAR γ is expressed primarily in adipose tissue; and PPAR δ is expressed ubiquitously. Studies of the individual PPAR isoforms and ligands have revealed their regulation of processes involved in insulin resistance and diabetes, as well as lipid disorders, such as hyperlipidemia and dyslipidemia. PPAR γ agonists, such as pioglitazone, can be useful in the treatment of non-insulin dependent diabetes mellitus. Such PPAR γ agonists are associated with insulin sensitization.

PPAR α agonists, such as fenofibrate, can be useful in the treatment of hyperlipidemia. Although clinical evidence is not available to reveal the utility of PPAR δ agonists in humans, several preclinical studies suggest that PPAR δ agonists can be useful in the treatment of diabetes and lipid disorders.

The prevalence of the conditions that comprise Metabolic Syndrome (obesity, insulin resistance, hyperlipidemia, hypertension and atherosclerosis) continues to increase. New pharmaceutical agents are
5 needed to address the unmet clinical needs of patients.

PPAR δ agonists have been suggested as a potential treatment for use in regulating many of the parameters associated with Metabolic Syndrome and Atherosclerosis. For example, in obese, non-diabetic rhesus monkeys, a
10 PPAR δ agonist reduced circulating triglycerides and LDL, decreased basal insulin levels and increased HDL (Oliver, W.R. et al. Proc Natl Acad Sci 98:5306-5311; 2001). The insulin sensitization observed with the use of a PPAR δ agonist is thought to be in part due to decreased
15 myocellular lipids (Dressel, U. et al. Mol Endocrinol 17:2477-2493; 2003).

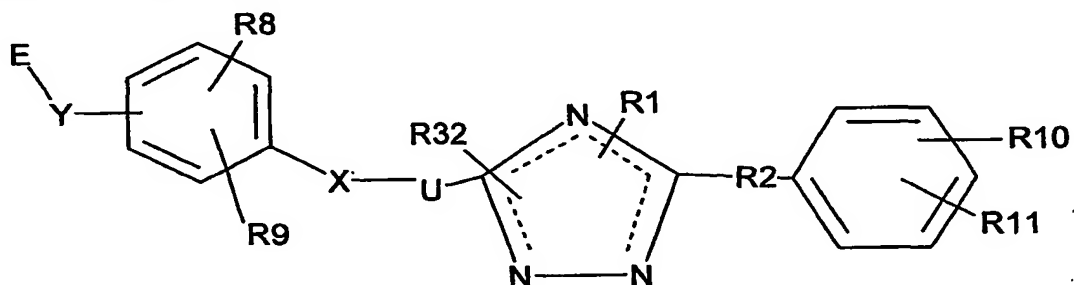
Further, atherosclerosis is considered to be a disease consequence of dyslipidemia and may be associated with inflammatory disease. C-reactive protein (CRP)
20 production is part of the acute-phase response to most forms of inflammation, infection and tissue damage. It is measured diagnostically as a marker of low-grade inflammation. Plasma CRP levels of greater than 3 mg/L have been considered predictive of high risk for coronary
25 artery disease (J. Clin. Invest 111: 1085-1812, 2003).

PPAR δ agonists are believed to mediate anti-inflammatory effects. Indeed, treatment of LPS-stimulated macrophages with a PPAR δ agonist has been observed to reduce the expression of iNOS, IL12, and IL-6
30 (Welch, J.S. et al. Proc Natl Acad Sci 100:6712-6717 2003).

It may be especially desirable when the active pharmaceutical agent selectively modulates a PPAR receptor subtype to provide an especially desirable pharmacological profile. In some instances, it can be desirable when the active pharmacological agent selectively modulates more than one PPAR receptor subtype to provide a desired pharmacological profile.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by the following structural Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-₄-alkyl, aryl-C₁-₄-heteroalkyl, heteroaryl-C₀-₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀-₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-₄-alkyl, aryl-C₁-₄-heteroalkyl, heteroaryl-C₀-₄-alkyl, C₃-C₆ cycloalkylaryl-C₀-₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

- 5 (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19, NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 10 (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- 15 (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- 20 (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- 25 (f) Y is selected from the group consisting of C, NH, and a single bond;
- (g) E is C(R3)(R4)A or A and wherein
- 30 (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each

optionally substituted with from one to two groups independently selected from R⁷;

(ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;

(iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and

(iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy,

aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;

(h) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;

(i) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

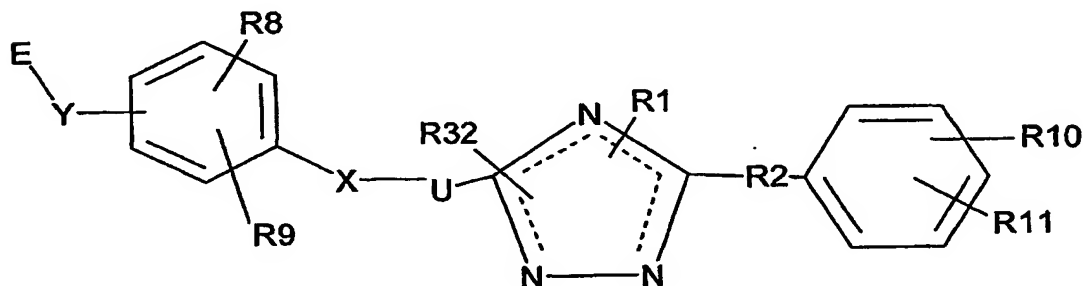
(j) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆

- alkylenyl, C₁-C₆ alkyl-COOR₁₂'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R₁₃', COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂, NR₁₈'C(O)R₁₉', NR₂₀'SO₂R₂₁', SR₂₂', S(O)R₂₃', S(O)₂R₂₄', and S(O)₂N(R₂₅')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R₁₂', R₁₂'', R₁₃', R₁₄', R₁₅', R₁₆', R₁₇', R₁₈', R₁₉', R₂₀', R₂₁', R₂₂', R₂₃', R₂₄', and R₂₅' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;

(m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and

(n) ---- is optionally a bond to form a double bond at the indicated position.

A further embodiment of the present invention is a compound of the Formula II:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C₃-C₆ cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12, C₁-C₆

- alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 5
- 10 (c) R₂ is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R₃₀;
- 15
- 20 (f) Y is selected from the group consisting of C, O, S, NH and a single bond;
- (g) E is C(R₃)(R₄)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- 25

(ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;

(iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and

(iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;

(h) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;

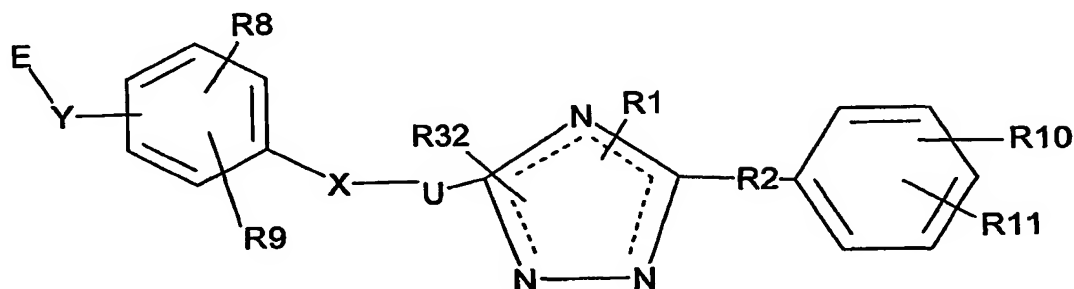
(i) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

(j) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR₁₂'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇

- cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C_{3-C6} cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R_{13'}, COOR_{14'}, OC(O)R_{15'}, OS(O)₂R_{16'}, N(R_{17'})₂, NR_{18'}C(O)R_{19'}, NR_{20'}SO₂R_{21'}, SR_{22'}, S(O)R_{23'}, S(O)₂R_{24'}, and S(O)₂N(R_{25'})₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C_{3-C6} cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R_{12'}, R_{12''}, R_{13'}, R_{14'}, R_{15'}, R_{16'}, R_{17'}, R_{18'}, R_{19'}, R_{20'}, R_{21'}, R_{22'}, R_{23'}, R_{24'}, and R_{25'} are each independently selected from the group consisting of hydrogen, C_{1-C6} alkyl and aryl;
- (l) R₃₀ is selected from the group consisting of C_{1-C6} alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C_{3-C6} cycloalkylaryl-C₀₋₂-alkyl, and wherein C_{1-C6} alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C_{3-C6} cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;
- (m) R₃₂ is selected from the group consisting of a bond, hydrogen, halo, C_{1-C6} alkyl, C_{1-C6} haloalkyl, and C_{1-C6} alkyloxo; and

(n) ---- is optionally a bond to form a double bond at the indicated position.

Another embodiment of the present invention is a compound of the Formula III:



5

and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- 10 (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-
- 15 C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C₃-C₆ cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- 20 (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀-4-alkyl,
- 25

- heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19, NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 5 (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- 10 (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- 15 (f) Y is selected from the group consisting of O, S, NH, C, and a single bond;
- 20 (g) E is C(R3)(R4)A; wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- 25 (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- 30

(iii) R3 is selected from the group consisting of C₁-C₅ alkyl, and C₁-C₅ alkoxy; and

(iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

with the proviso that when Y is O then R4 is selected from the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

(h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;

(i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29

is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

(j) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR_{12''}, C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R_{13'}, COOR_{14'}, OC(O)R_{15'}, OS(O)₂R_{16'}, N(R_{17'})₂, NR_{18'}C(O)R_{19'}, NR_{20'}SO₂R_{21'}, SR_{22'}, S(O)R_{23'}, S(O)₂R_{24'}, and S(O)₂N(R_{25'})₂; and wherein aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;

(k) R_{12'}, R_{12''}, R_{13'}, R_{14'}, R_{15'}, R_{16'}, R_{17'}, R_{18'}, R_{19'}, R_{20'}, R_{21'}, R_{22'}, R_{23'}, R_{24'}, and R_{25'} are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

(l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl,

heteroaryl-C₀₋₄-alkyl, and C₃₋₆
cycloalkylaryl-C₀₋₂-alkyl are each optionally
substituted with from one to three substituents
each independently selected from R₃₁;

- 5 (m) R₃₂ is selected from the group consisting of a
bond, hydrogen, halo, C₁₋₆ alkyl, C₁₋₆
haloalkyl, and C₁₋₆ alkyloxy; and
(n) ---- is optionally a bond to form a double bond
at the indicated position.

10

In one embodiment, the present invention also
relates to pharmaceutical compositions comprising at
least one compound of the present invention, or a
pharmaceutically acceptable salt, solvate, hydrate, or
15 stereoisomer thereof, and a pharmaceutically acceptable
carrier.

In another embodiment, the present invention relates
to a method of selectively modulating a PPAR delta
receptor by contacting the receptor with at least one
20 compound represented by Structural Formula I, or a
pharmaceutically acceptable salt, solvate, hydrate, or
stereoisomer thereof.

In another embodiment, the present invention relates
to a method of modulating one or more of the PPAR alpha,
25 beta, gamma, and/or delta receptors.

In a further embodiment, the present invention
relates to a method of making a compound represented by
Structural Formula I.

The compounds of the present invention are believed
30 to be effective in treating and preventing Metabolic
Disorder, Type II diabetes, hyperglycemia,

hyperlipidemia, obesity, coagulopathy, hypertension, atherosclerosis, and other disorders related to Metabolic Disorder and cardiovascular diseases. Further, compounds of this invention can be useful for lowering fibrinogen, increasing HDL levels, treating renal disease, controlling desirable weight, treating demyelinating diseases, treating certain viral infections, and treating liver disease. In addition, the compounds can be associated with fewer clinical side effects than compounds currently used to treat such conditions.

DETAILED DESCRIPTION OF THE INVENTION

The terms used to describe the instant invention have the following meanings.

As used herein, the term "aliphatic linker" or "aliphatic group" is a non-aromatic, consisting solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double and/or triple bonds (also refer herein as "alkenyl" and "alkynyl"). An aliphatic or aliphatic group may be straight chained, branched (also refer herein as "alkyl") or cyclic (also refer herein as "cycloalkyl"). When straight chained or branched, an aliphatic group typically contains between about 1 and about 10 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an aliphatic typically contains between about 3 and about 10 carbon atoms, more typically between about 3 and about 7

carbon atoms. Aliphatics are preferably C₁-C₁₀ straight chained or branched alkyl groups (i.e. completely saturated aliphatic groups), more preferably C₁-C₆ straight chained or branched alkyl groups. Examples
5 include, but are not limited to methyl, ethyl, propyl, n-propyl, iso-propyl, n-butyl, sec-butyl, and tert-butyl. Additional examples include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cyclopentyl, cyclohexyl and the like. Such aliphatic linker is
10 optionally substituted with from one to four substituents each independently selected from R₃₀. It can be preferred that aliphatic linker is substituted with from zero to two substituents each independently selected from R₃₀. Further, it may be preferred that one carbon of the
15 aliphatic linker is replaced with an O, NH, or S.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated configuration. As used herein, "C₀ alkyl" means that
20 there is no carbon and therefore represents a bond. Examples of "alkyl" include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, pentyl, hexyl, isopentyl and the like. Alkyl as defined above may be optionally
25 substituted with a designated number of substituents as set forth in the embodiment recited above. As used

herein, the term "alkyloxo" means an alkyl group of the designated number of carbon atoms with a "=O" substituent.

The term "alkenyl" or "alkylenyl" means
5 hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon double bond, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl, 2-butenyl and the like.
10 Alkenyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "alkynyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or
15 branched configuration and having at least one carbon-carbon triple bond, which may occur at any point along the chain. Example of alkynyl is acetylene. Alkynyl as defined above may be optionally substituted with designated number of substituents as set forth in the
20 embodiment recited above.

The term "heteroalkyl" refers to a means hydrocarbon chain of a specified number of carbon atoms wherein at least one carbon is replaced by a heteroatom selected from the group consisting of O, N and S.

25 The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, typically 3 to 7 carbon atoms. Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl,
30 cyclohexyl and cycloheptyl, and the like. "Cycloalkyaryl" means that an aryl is fused with a

cycloalkyl, and "Cycloalkylaryl-alkyl" means that the cycloalkylaryl is linked to the parent molecule through the alkyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a C₁-C₆ alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. An example of a haloalkyl group is trifluoromethyl (CF₃).

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "haloalkyloxy" represents a C₁-C₆ haloalkyl group attached through an oxygen bridge, such as OCF₃. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). "Aryl" as defined above may be optionally substituted with a

designated number of substituents as set forth in the embodiment recited above.

The term "arylalkyl" refers to an aryl alkyl group which is linked to the parent molecule through the alkyl group, which may be further optionally substituted with a designated number of substituents as set forth in the embodiment recited above. When arylalkyl is arylC₀alkyl, then the aryl group is bonded directly to the parent molecule. Likewise, arylheteroalkyl means an aryl group linked to the parent molecule through the heteroalkyl group.

The term "acyl" refers to alkylcarbonyl, arylcarbonyl, and heteroarylcarbonyl species.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from the group consisting of O, N, and S. The "heteroaryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heteroaryl are, but are not limited to, furanyl, indolyl, thienyl (also referred to herein as "thiophenyl") thiazolyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzothienyl, benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline and the like. The term "heteroarylalkyl" means that the heteroaryl group is linked to the parent

molecule through the alkyl portion of the heteroarylalkyl.

The term "heterocycloalkyl" refers to a non-aromatic ring which contains one or more oxygen, nitrogen or sulfur and includes a monocyclic, bicyclic or tricyclic non-aromatic ring of 5 to 14 carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocycloalkyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocycloalkyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine. As used herein, alkyl groups include straight chained and branched hydrocarbons, which are completely saturated.

As used herein, the phrase "selectively modulate" means a compound whose EC50 for the stated PPAR receptor is at least ten fold lower than its EC50 for the other PPAR receptor subtypes.

PPAR δ has been proposed to associate with and dissociate from selective co-repressors (BCL-6) that control basal and stimulated anti-inflammatory activities (Lee, C-H. et al. Science 302:453-4572003). PPAR δ agonists are thought to be useful to attenuate other inflammatory conditions such as inflammation of the joints and connective tissue as occurs in rheumatoid arthritis, related autoimmune diseases, osteoarthritis, as well as myriad other inflammatory diseases, Crohne's disease, and psoriasis.

When a compound represented by Structural Formula I has more than one chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may

be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated using methods familiar to the skilled artisan.

5 The present invention includes each diastereoisomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted
10 rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Structural Formula I and mixtures thereof.

15 Certain compounds of Structural Formula I may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of Structural Formula I and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts
20 of the compounds of the Structural Formula I which are considered to be acceptable for clinical and/or veterinary use. Typical pharmaceutically-acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or
25 organic acid or an organic or inorganic base. Such salts are known as acid addition salts and base addition salts, respectively. It will be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the
30 salt as a whole is pharmaceutically-acceptable and as long as the counterion does not contribute undesired

qualities to the salt as a whole. These salts may be prepared by methods known to the skilled artisan.

The term, "active ingredient" means the compounds generically described by Structural Formula I as well as
5 the stereoisomers, salts, solvates, and hydrates,

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients and salt are pharmaceutically compatible with the other ingredients of the composition. Pharmaceutical compositions of the
10 present invention are prepared by procedures known in the art using well known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein. The term
15 "preventing" is particularly applicable to a patient that is susceptible to the particular pathological condition.

"Treating" refers to mediating a disease or condition and preventing, or mitigating, its further progression or ameliorate the symptoms associated with
20 the disease or condition.

"Pharmaceutically-effective amount" means that amount of active ingredientit, that will elicit the biological or medical response of a tissue, system, or mammal. Such an amount can be administered
25 prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to
30 include an amount which is sufficient to modulate a selected PPAR receptor or to prevent or mediate a disease

or condition. Generally, the effective amount of a Compound of Formula I will be between 0.02 through 5000 mg per day. Preferably the effective amount is between 1 through 1,500 mg per day. Preferably the dosage is from 1 through 1,000 mg per day. A most preferable the dose can be from 1 through 100 mg per day.

The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals.

10 A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

Administration to a human is most preferred. The compounds and compositions of the present invention are useful for the treatment and/or prophylaxis of cardiovascular disease, for raising serum HDL cholesterol levels, for lowering serum triglyceride levels and for lower serum LDL cholesterol levels. Elevated triglyceride and LDL levels, and low HDL levels, are risk factors for the development of heart disease, stroke, and circulatory system disorders and diseases.

Further, the compound and compositions of the present invention may reduce the incidence of undesired cardiac events in patients. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

30 The compounds and compositions of the present invention are also useful for treating and/or preventing obesity.

Further, these compounds and compositions are useful for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus (NIDDM) with reduced or no body weight gains by the patients. Furthermore, the
5 compounds and compositions of the present invention are useful to treat or prevent acute or transient disorders in insulin sensitivity, such as sometimes occur following surgery, trauma, myocardial infarction, and the like. The physician of ordinary skill will know how to identify
10 humans who will benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering
15 an effective amount of active ingredient, as defined herein, to a hyperglycemic human or non-human mammal in need thereof.

The invention also relates to the use of a compound of Formula I as described above, for the manufacture of a
20 medicament for treating a PPAR receptor mediated condition.

A therapeutically effective amount of a compound of Structural Formula I can be used for the preparation of a medicament useful for treating Metabolic Disorder,
25 diabetes, treating obesity, lowering tryglyceride levels, lowering serum LDL levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or
30 subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically

effective amount of a compound of the present invention typically reduces serum triglyceride levels of a patient by about 20% or more, and increases serum HDL levels in a patient. Preferably, HDL levels will be increased by
5 about 30% or more. In addition, a therapeutically effective amount of a compound, used to prevent or treat NIDDM, typically reduces serum glucose levels, or more specifically HbA1c, of a patient by about 0.7% or more.

When used herein Metabolic Syndrome
10 includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and
15 treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent
20 diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially atherosclerosis. In addition, the methods and treatments mentioned herein include the above and encompass the treatment and/or
25 prophylaxis of any one of or any combination of the following inflammatory and autoimmune diseases: adult respiratory distress syndrome, rheumatoid arthritis, demyelinating disease, Crohn's disease, asthma, systemic lupus erythematosus, psoriasis, and bursitis.
30 The compositions are formulated and administered in the same general manner as detailed herein. The

compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of
5 a single pharmaceutical dosage composition which contains a compound of Structural Formula I, a stereoisomer, salt, solvate and/or hydrate thereof ("Active Ingredient") and one or more additional active agents, as well as administration of a compound of Active Ingredient and
10 each active agent in its own separate pharmaceutical dosage formulation. For example, an Active Ingredient and an insulin secretagogue such as biguanides, thiazolidinediones, sulfonylureas, insulin, or α -glucosidase inhibitors can be administered to the patient
15 together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, an Active Ingredient and one or more additional active agents can be administered at
20 essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of
25 atherosclerosis may be wherein an Active Ingredient is administered in combination with one or more of the following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As
30 noted above, the Active Ingredient can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the Active Ingredient can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α -glucosidase inhibitors, other insulin secretagogues, insulin as well as the active agents discussed above for treating atherosclerosis.

The Active Ingredients of the present invention, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of Active Ingredient of the present invention, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the Active Ingredient of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the Active Ingredient of the present invention, calculated to produce the desired therapeutic effect, in association with one or more

pharmaceutically-acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1500 milligrams or more according to the particular treatment involved. It may
5 be preferred that the unit dosage is from about 1 mg to about 1000 mg.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of
10 factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the
15 particular compound and salt thereof employed, and the like.

Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit
20 containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of the compound or compounds of Structural Formula I actually to be administered will be determined by a physician, in the light of all the relevant
25 circumstances.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via
30 transdermal forms, of course, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery (bolus or
5 infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraven-tricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the invention can also be administered in a targeted drug
10 delivery system, such as, for example, in a liposome coated with endothelial cell-specific antibody.

Solid form formulations include powders, tablets and capsules.

Sterile liquid formulations include suspensions,
15 emulsions, syrups, and elixirs.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying,
20 encapsulating, entrapping or lyophilizing processes.

The following pharmaceutical formulations 1 and 2 are illustrative only and are not intended to limit the scope of the invention in any way.

25 Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200

Magnesium stearate	<u>10</u>
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity <u>(mg/tablet)</u>
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

5

The components are blended and compressed to form tablets each weighing 665 mg .

In yet another embodiment of the compounds of the present invention, the compound is radiolabelled, such as
10 with carbon-14, or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new selective PPAR receptor agonists.

The compounds of the present invention can be
15 useful for modulating insulin secretion and as research tools. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be
20 independently combined to produce a variety of preferred compounds and process conditions. The following list of

embodiments of this invention is not intended to limit the scope of this invention in any way.

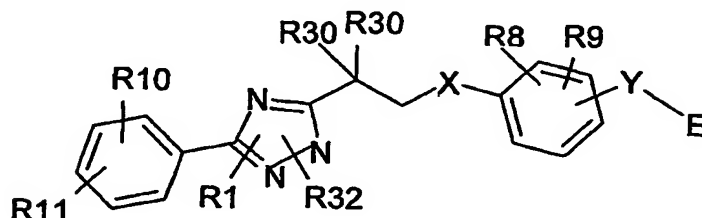
Some preferred characteristics of compounds of formula I are:

- 5 (a) R3 is methyl;
- (b) R4 is hydrogen;
- (c) R3 and R4 are each hydrogen;
- (d) R3 and R4 are each methyl;
- (e) A is carboxyl;
- 10 (f) X is -O-;
- (g) X is -S-;
- (h) U is CH;
- (i) U is CH₂CH;
- (j) R9 is methyl;
- 15 (k) R9 is hydrogen;
- (l) R9 is C₁-C₃ alkyl;
- (m) R8 is methyl;
- (n) R8 and R9 are each hydrogen;
- (o) R10 is CF₃;
- 20 (p) R10 is haloalkyl;
- (q) R10 is haloalkyloxy;
- (r) R11 is hydrogen
- (s) R10 and R11 are each hydrogen;
- (t) R11 is haloalkyl;
- 25 (u) R10 and R11 combine to form a fused bicyclic;
- (v) R10 and R11 combine to form a naphthyl substituent with the phenyl to which they are attached;
- 30 (w) R1 is optionally substituted C₂-C₃ arylalkyl;

- (x) R1 is substituted C2 arylalkyl;
- (y) ---- in the five membered ring each
form a double bond at the designated
position in Formula I;
- 5 (z) R1 is C₁-C₄ alkyl;
- (aa) R32 is hydrogen;
- (bb) R2 is a bond;
- (cc) R2 is C₁-C₂ alkyl;
- (dd) Y is O;
- 10 (ee) Y is S;
- (ff) Y is C;
- (gg) Y is C, NH, or a bond;
- (hh) E is C(R3)(R4)A;
- (ii) R3 is hydrogen;
- 15 (jj) R3 is C₁-C₂ alkyl;
- (kk) R4 is C₁-C₂ alkyl;
- (ll) R3 and R4 are each hydrogen;
- (mm) R3 and R4 are each methyl;
- (nn) A is COOH;
- 20 (oo) Aliphatic linker is saturated;
- (pp) Aliphatic linker is substituted with
C₁-C₃ alkyl;
- (qq) Aliphatic linker is substituted with
from one to three substituents each
independently selected from R30;
- 25 (rr) Aliphatic linker is substituted with
from one to two substituents each
independently selected from R30;
- (ss) Aliphatic linker is C₁-C₃ alkyl;
- 30 (tt) Aliphatic linker is C₁-C₂ alkyl;

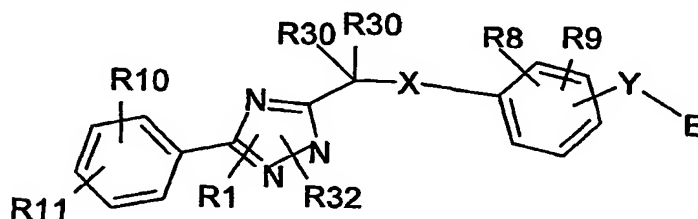
(uu) Aliphatic linker is C₁-C₃ alkyl and one carbon is replaced with an -O-;

(vv) A compound of Formula II:

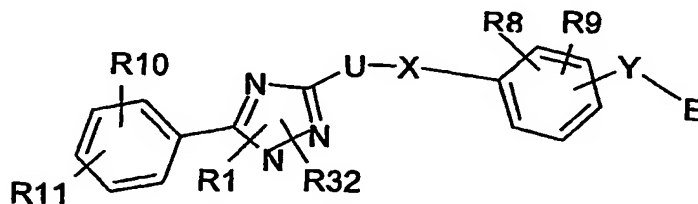


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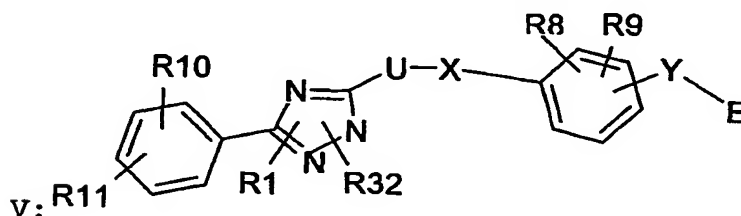
(ww) A compound of Structural Formula III:



(xx) A compound of Structural Formula IV:

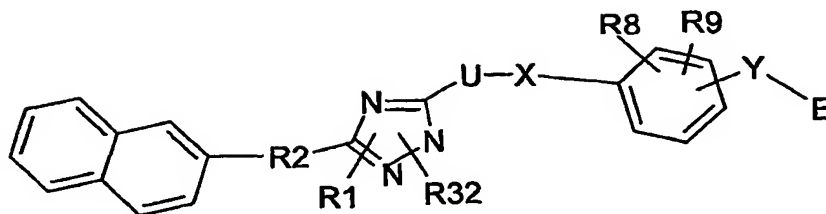


(yy) A compound of Structural Formula

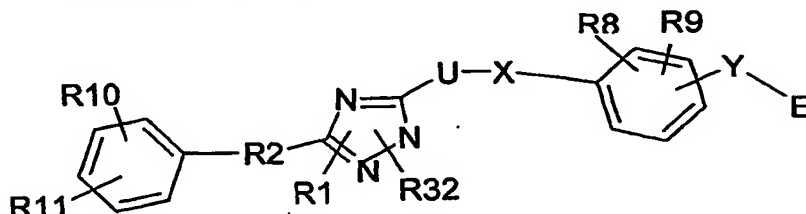


10

(zz) A compound of Structural Formula:



(aaa) A compound of Structural Formula:



5

(bbb)

(ccc) Aryl is a phenyl group;

(ddd) Aryl is a naphthyl group;

10

(eee) A compound of Formula I that selectively modulates a delta receptor;

(fff) An Active Ingredient, as described herein, that is a PPAR coagonist that modulates a gamma receptor and a delta receptor;

15

(ggg) An Active Ingredient, as described herein, for use in the treatment of cardiovascular disease;

(hhh) An Active Ingredient, as described herein, for use in the treatment of Metabolic Disorder;

20

(iii) An Active Ingredient for use in the control of obesity;

(jjj) An Active Ingredient for use in treating diabetes;

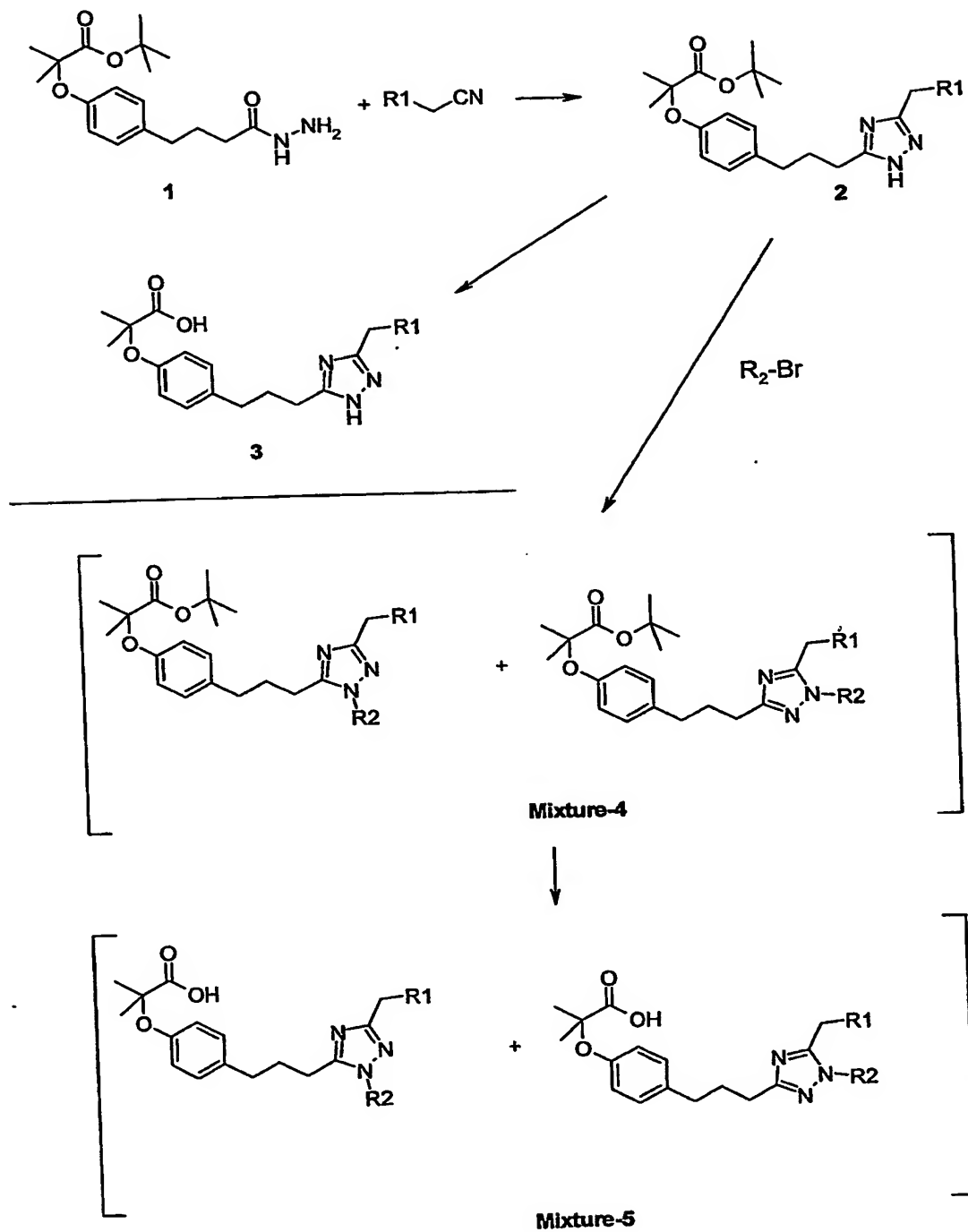
(kkk) An Active Ingredient that is a PPAR receptor agonist;

5 (lll) A compound of Formula I selected from the group consisting of 2-Methyl-2-{4-[3-(5-naphthalen-2-ylmethyl-2H-[1,2,4]triazol-3-yl)-phenoxy}propionic acid.

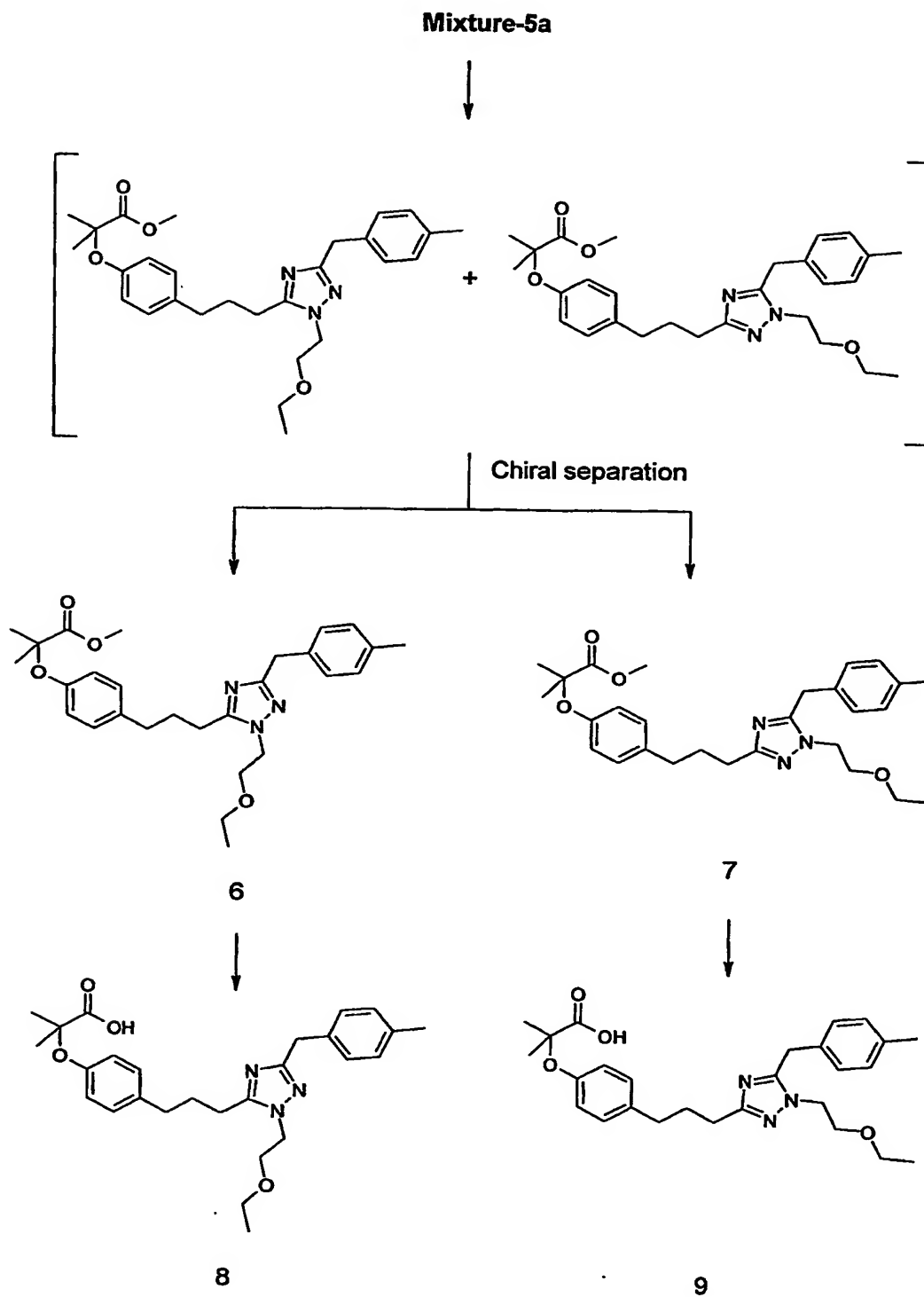
10 SYNTHESIS

Compounds of the present invention have been formed as specifically described in the examples. Further, many compounds are prepared as more generally using a) alkylation of phenol/thiophenol with a halide, b) a
15 Mitsunobu protocol (O. Mitsunobu, 1981 Synthesis, p1); c) and other methods known to the skilled artisan. Alternative synthesis methods may also be effective and known to the skilled artisan.

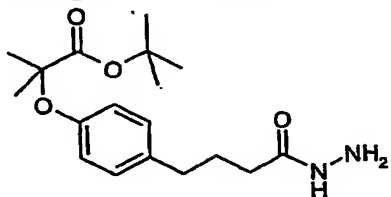
Scheme 1.



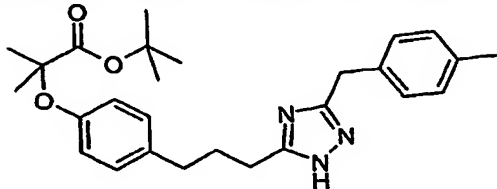
Scheme 2.



Example 1 (Compound 1)



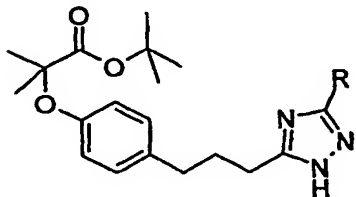
Example 2a (Compound 2a)



- 5 The hydrazide 1 (1.34 gm, 4 mmol) is taken up in methanol (30 mL). To this solution is added 4-methylbenzyl nitrile (1.04 gm, 8 mmole), followed by sodium methoxide (75 mg). The reaction is heated at reflux (~80°C) with stirring
- 10 for 24 h. The mixture is diluted with ethyl acetate (50 mL). Ethyl acetate is washed with water (3 x 60 mL), dried (Na₂SO₄), and concentrated on a rotovap to give an oily residue. The residue is purified on a silica column to give 2a as an oil (670 mg).
- 15 m/z: M+1 450.

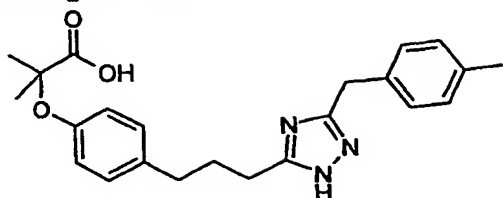
Examples 2b-2d:

- Compounds 2b to 2d shown in the following Table were synthesized according to the procedure for 2a, from 1
- 20 using appropriate nitrile shown in Table below.



Compound #	R	Nitrile Used	(m/z) M+1
2b	Phenethyl	2- Phenylpropionitrile	450
2c	Naphthylmethyl	2- Naphthylacetonitrile	486
2d	3-(4- Chlorophenyl)- 3-ethoxypropyl	4-(4-Chlorophenyl)- 4- ethoxybutyronitrile	542

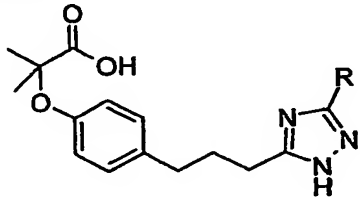
Example 3a.



The triazole **2a** (120 mg) is taken up in 50% TFA-dichloromethane (5 mL). This mixture is stirred at room temperature for 18 h. The solvent is removed on a rotovap and the residue is dried under high vacuum to give an oil (101 mg).
m/z: 394 (M+1).

10 Examples 3b-3d

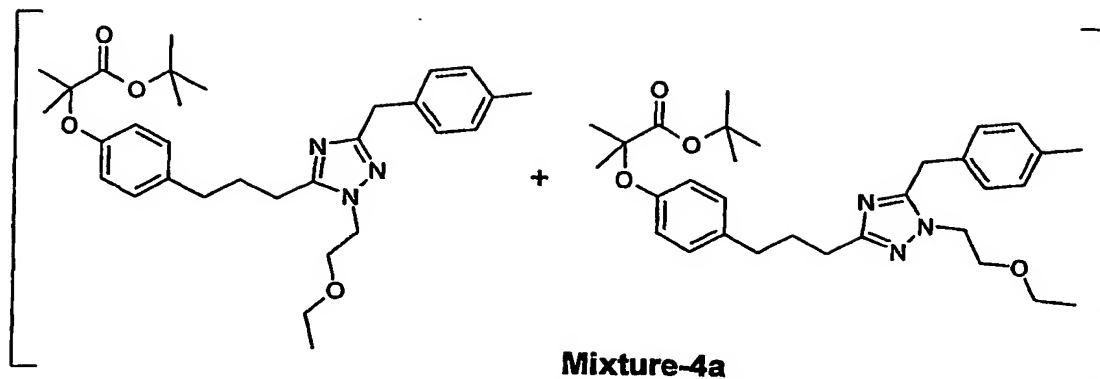
Compounds **3b** to **3c** shown in the following Table were synthesized according to the procedure for **3a**, using TFA mediated hydrolysis of appropriate t-butyl esters **2b** to **2d**.



15

Compound #	R	(m/z) M+1
3b	Phenethyl	394
3c	Naphthylmethyl	430
3d	3-(4-Chlorophenyl)-3-ethoxypropyl	486

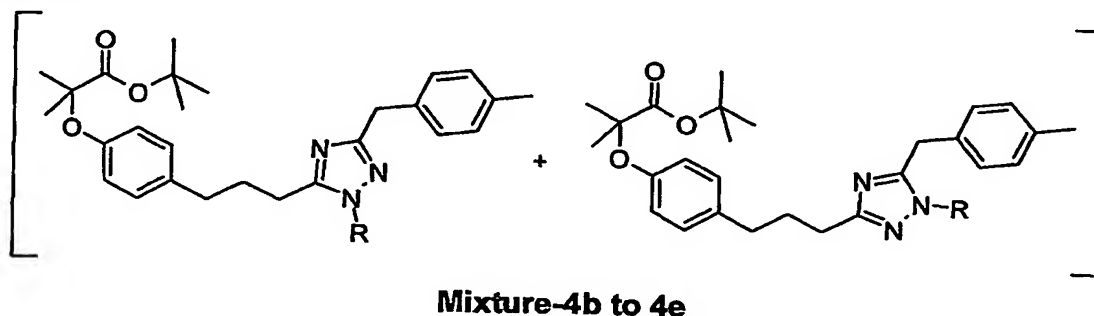
Example 4a:



To a solution of **2a** (70 mg) in anhydrous DMF (1.5 mL) is added 2-ethoxyethylbromide (0.1 mL) followed by anhydrous powdered K_2CO_3 . The reaction mixture is heated at 50°C with stirring for 18 h. The mixture is diluted with ethyl acetate (30 mL) and ethyl acetate is washed with water (3 x 30 mL). Ethyl acetate layer is dried (Na_2SO_4), and concentrated on a rotovap to give an oily residue. The residue is purified on a silica column to give approximate 40-60 regio-isomeric mixture of **4a** as an oil (62 mg).
 m/z: 522 (M+1).

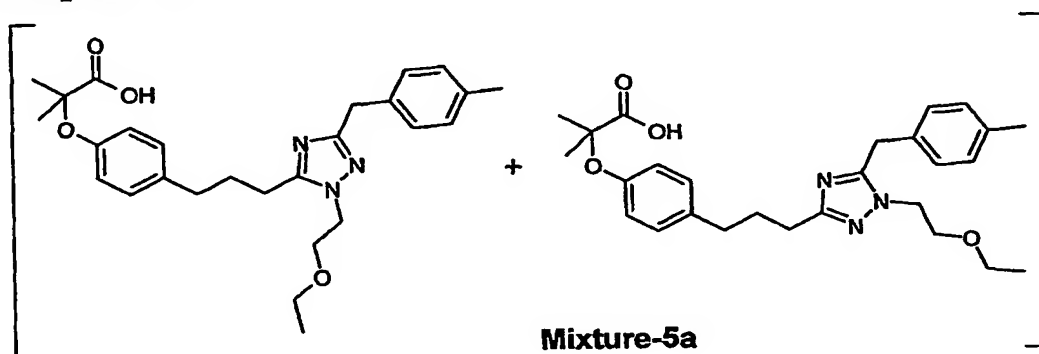
Examples 4b to 4f.

Compounds **4b** to **4f** shown in the following Table were synthesized according to the procedure for **4a**, from **2a** using appropriate alkylbromide as shown in Table below.



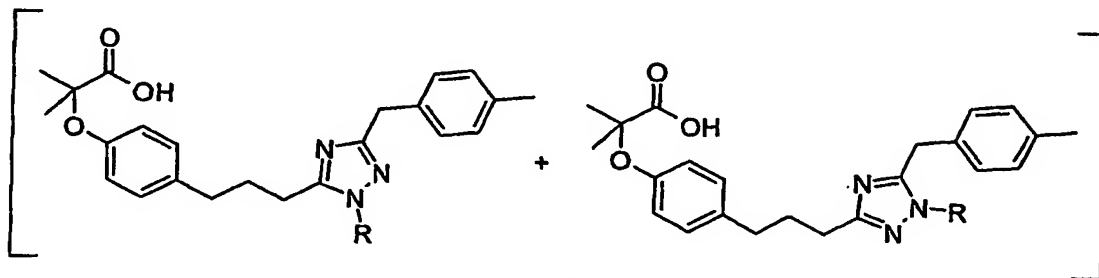
Compnd #	R	Alkylbromide Used	(m/z) M+1
4b	2-(2-methoxy)ethoxyethyl	2-(2-methoxy)ethoxyethylbromide	552
4c	3-tetrahydropyranoxypropyl	3-tetrahydropyranoxypropyl bromide	592
4d	6-tetrahydropyranoxyhexyl	6-tetrahydropyranoxyhexylbromide	634
4e	4-t-butylbenzyl	4-t-butylbenzylbromide	596
4f	2-Oxobutyl	1-Bromobutan-2-one	520

5 **Example 5a:**



The triazole **mixture-4a** (61 mg) is taken up in 50% TFA-dichloromethane (4 mL). This mixture is stirred at room temperature for 4 h. The solvent is removed on a rotovap and the residue is dried under high vacuum to give regioisomeric **mixture 5a** an oil (30 mg). m/z: 466 (M+1)

Examples 5b to 5e.



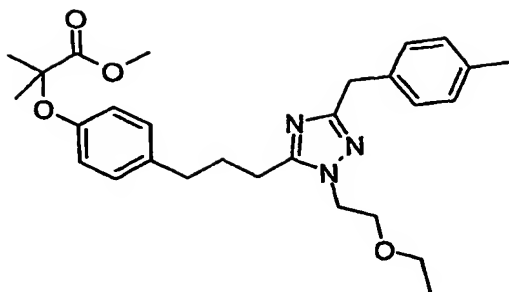
5

Compound #	R	(m/z) M+1
5b	2-(2-methoxy)ethoxyethyl	496
5c	3-hydroxypropyl	452
5d	6-hydroxyhexyl	494
5e	4-t-butylbenzyl	540
5f	2-Oxobutyl	464

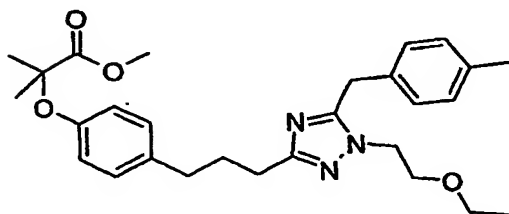
To a solution of **mixture-5a** (70 mg) in methanol (25 mL) is added conc. H₂SO₄. The reaction mixture is stirred at room temperature for 18 h. Solvent is removed to a small volume and the residue is diluted with ethyl acetate (30 mL). Ethyl acetate layer is washed with water (3 x 30 mL), dried (Na₂SO₄), and concentrated on a rotovap to give an oily residue (71 mg). The residue is purified on a chiral HPLC column to give pure **6** and **7**.

6: (15 mg), m/z: 480 (M+1).

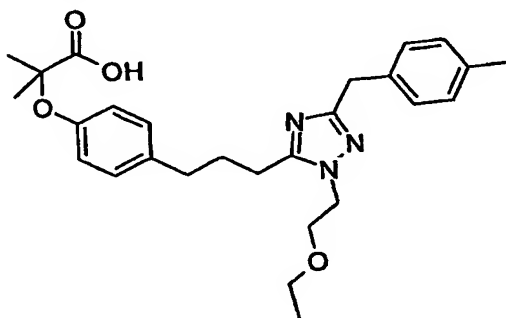
15 6: (15 mg), m/z: 480 (M+1).



7: (19 mg), m/z : 480 ($M+1$).



Example 8.



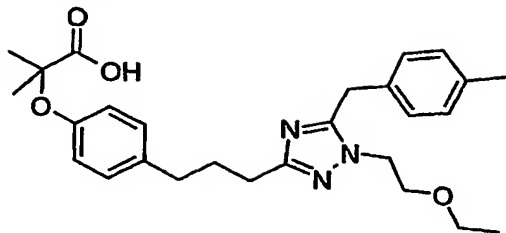
5

Triazole ester 6 (15 mg) is taken up in methanol (2 mL). To this solution is added 2N aqueous NaOH (1mL). The mixture is stirred at room temperature for 2 h. The solvent is evaporated on the rotovap and the residue is dissolved in water (5 mL). The solution is acidified to pH ~3 with 0.1 M aqueous HCl to give a milky solution. The mixture is extracted with CH_2Cl_2 (3 x 10 mL). Combined CH_2Cl_2 layer is dried (Na_2SO_4), and concentrated on a rotovap and then dried under high vacuum to give acid 8 (11 mg). m/z : 466 ($M+1$).

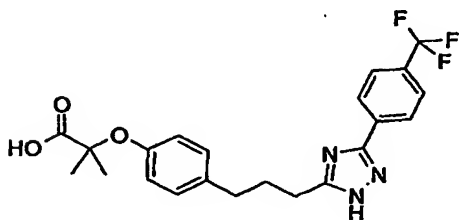
10

15

Example 9.

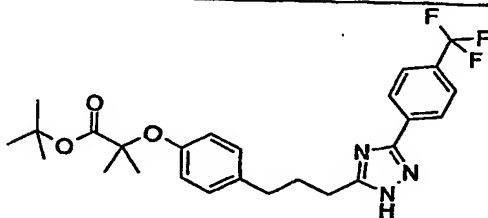


Acid 9 is synthesized according to the procedure for 8,
5 by NaOH mediated hydrolysis of ester 6. m/z: 466 (M+1).



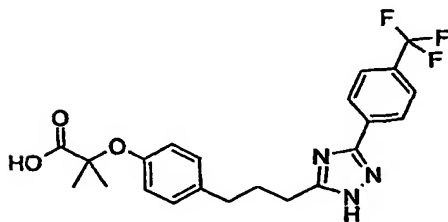
Example 10

Synthesis of 2-Methyl-2-(4-{3-[5-(4-trifluoromethyl-phenyl)-2H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid.



Step 1: Synthesis of 2-Methyl-2-(4-{3-[5-(4-trifluoromethyl-phenyl)-2H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid tert-butyl ester . To a solution of 2-[4-(3-Hydrazinocarbonyl-propyl)-phenoxy]-2-methyl-propionic acid tert-butyl ester (0.5 g, 1.5 mmol) in MeOH (5 mL), 4-(trifluoromethyl)benzonitrile (0.51 g, 3.0 mol) and potassium tert-butoxide (0.023 g, 0.21 mmol) are added. The mixture is stirred at reflux overnight. An additional 0.2 equivalents of potassium tert-butoxide are added and the reaction stirred for 24 h. The crude is quenched with water, the MeOH is removed in vacuo and the aqueous layer is extracted with EtOAc. The organic layer is separated, dried with MgSO₄, and is concentrated in

vacuo. The crude is purified by Biotage (Hexane/EtOAc 4:1) yielding 0.32 g (44 %) of the title compound, 2-Methyl-2-(4-{3-[5-(4-trifluoromethyl-phenyl)-2H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid tert-butyl ester as a pale yellow oil. MS Data (ES⁺)
5 m/z 490.6 [M + H]



10 Step 2. Synthesis of 2-Methyl-2-(4-{3-[5-(4-trifluoromethyl-phenyl)-2H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid. To a solution of the Step 1 product, 2-Methyl-2-(4-{3-[5-(4-trifluoromethyl-phenyl)-2H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-
15 propionic acid tert-butyl ester (0.65 g, 1.33 mmol) in CH₂Cl₂ (6.5 ml), TFA (0.31 mL, 3.98 mmol) is added. The mixture is stirred at r.t. overnight. By T.L.C. a significant amount of starting material remains. The solvent and residual TFA is removed in vacuo. The crude
20 is purified by flash column chromatography (Hexane/EtOAc 2:1 and 1:1) yielding 0.16 g (28 %) of the title compound as a white solid, and 0.4 g of the Step 2 starting material recovered. MS Data (ES⁺) m/z 434.3 [M + H].

Biological Assays

25 Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPAR α receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using SPA technology with PPAR receptors. Tritium-
30 labeled PPAR α agonists are used as radioligands for generating displacement curves and IC₅₀ values with

compounds of the invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs are
5 constitutively expressed using plasmids containing the CMV promoter. For PPAR α , interference by endogenous PPAR γ in CV-1 cells is an issue. In order to eliminate such interference, a GAL4 chimeric system is used in which the DNA binding domain of the transfected PPAR is
10 replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Cotransfection efficacy is determined relative to PPAR α agonist reference molecules. Efficacies are determined by computer fit to a concentration-response curve, or in
15 some cases at a single high concentration of agonist (10 μ M).

These studies are carried out to evaluate the ability of compounds of the invention to bind to and/or activate various nuclear transcription factors,
20 particularly huPPAR α ("hu" indicates "human"). These studies provide in vitro data concerning efficacy and selectivity of compounds of the invention. Furthermore, binding and cotransfection data for compounds of the invention are compared with corresponding data for
25 marketed compounds that act on huPPAR α .

The binding and cotransfection efficacy values for compounds of the invention which are especially useful for modulating a PPAR receptor, are \leq 100 nM and \geq 50%, respectively.

Evaluation of Triglyceride Reduction and HDL Cholesterol
Elevation in HuapoAI Transgenic Mice

Compounds of the present invention are studied for effects upon HDL and triglyceride levels in human apoAI mice. For each compound tested, seven to eight week old male mice, transgenic for human apoAI (C57BL/6-tgn(apoal)1rub, Jackson Laboratory, Bar Harbor, ME) are acclimated in individual cages for two weeks with standard chow diet (Purina 5001) and water provided ad libitum. After the acclimation, mice and chow are weighed and assigned to test groups (n = 5) with randomization by body weight. Mice are dosed daily by oral gavage for 8 days using a 29 gauge, 1-1/2 inch curved feeding needle (Popper & Sons). The vehicle for the controls, test compounds and the positive control (fenofibrate 100mg/kg) is 1% carboxymethylcellulose (w/v) with 0.25% tween 80 (w/v). All mice are dosed daily between 6 and 8 a.m. with a dosing volume of 0.2ml. Prior to termination, animals and diets are weighed and body weight change and food consumption are calculated. Three hours after last dose, mice are euthanized with CO₂ and blood is removed (0.5-1.0 ml) by cardiac puncture. After sacrifice, the liver, heart, and epididymal fat pad are excised and weighed. Blood is permitted to clot and serum is separated from the blood by centrifugation.

Cholesterol and triglycerides are measured colorimetrically using commercially prepared reagents (for example, as available from Sigma #339-1000 and Roche #450061 for triglycerides and cholesterol, respectively). The procedures are modified from published work (McGowan M. W. et al., Clin Chem 29:538-542, 1983; Allain C. C. et

al., Clin Chem 20:470-475,1974. Commercially available standards for triglycerides and total cholesterol, respectively, commercial quality control plasma, and samples are measured in duplicate using 200 μ l of reagent. An additional aliquot of sample, added to a well containing 200 μ l water, provided a blank for each specimen. Plates are incubated at room temperature on a plate shaker and absorbance is read at 500 nm and 540 nm for total cholesterol and triglycerides, respectively. Values for the positive control are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol quantitated by fast protein liquid chromatography (FPLC) coupled to an in line detection system. Samples are applied to a Superose 6 HR size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16ml/min mixed with the column effluent through a T-connection and the mixture passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37 C water bath. The colored product produced in the presence of cholesterol is monitored in the flow stream at 505 nm and the analog voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted vs time and the area under the curve corresponding to the elution of very low density

lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) is calculated using Perkin Elmer Turbochrome software.

5 Triglyceride Serum Levels in Mice Dosed with a Compound of the Invention is Compared to Mice Receiving the Vehicle to identify compounds which could be particularly useful for lowering triglycerides. Generally, triglyceride decreases of greater than or equal to 30% (thirty percent) compared to control
10 following a 30 mg/kg dose suggests a compound that can be especially useful for lowering triglyceride levels.

The percent increase of HDLc serum levels in mice receiving a compound of the invention is compared to mice receiving vehicle to identify compounds of the invention
15 that could be particularly useful for elevating HDL levels. Generally, and increase of greater than or equal to 25% (twenty five percent) increase in HDLc level following a 30 mg/kg dose suggests a compound that can be especially useful for elevating HDLc levels.

20 It may be particularly desirable to select compounds of this invention that both lower triglyceride levels and increase HDLc levels. However, compounds that either lower triglyceride levels or increase HDLc levels may be desirable as well.

25

Evaluation of Glucose Levels in db/db Mice

The effects upon plasma glucose associated with administering various dose levels of different compounds of the present invention and the PPAR gamma agonist
30 rosiglitazone (BRL49653) or the PPAR alpha agonist

fenofibrate, and the control, to male db/db mice, are studied.

Five week old male diabetic (db/db) mice [for example, C57BlKs/j-m +/- Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates are housed 6 per cage with food and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed, and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube. Sample is discharged into a heparinized microtainer with gel separator and retained on ice. Plasma is obtained after centrifugation at 4°C and glucose measured immediately. Remaining plasma is frozen until the completion of the experiment, when glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the following morning, mice are dosed daily by oral gavage for 7 days. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After the 24-hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane and

blood obtained via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

Glucose is measured colorimetrically using commercially purchased reagents. According to the manufacturers, the procedures are modified from published work (McGowan, M. W., Artiss, J. D., Strandbergh, D. R. & Zak, B. Clin Chem, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte, coupled with a color reaction first described by Trinder (Trinder, P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified in our laboratory for use in a 96 well format. The commercially available standard for glucose, commercially available quality control plasma, and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature for 18 minutes for glucose on a plate shaker (DPC Micormix 5) and absorbance read at 500 nm on a plate reader. Sample absorbances are

compared to a standard curve (100-800 for glucose). Values for the quality control sample are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are
5 assayed at the same time to minimize inter-assay variability.

Evaluation of the Effects of Compounds of the Present
Invention upon A^y Mice Body Weight, Fat Mass, Glucose and
Insulin Levels

10

Female A^y Mice

Female A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the
15 duration of the study. At twenty weeks of age the mice are randomly assigned to vehicle control and treated groups based on body weight and body fat content as assessed by DEXA scanning (N=6). Mice are then dosed via
20 oral gavage with either vehicle or a Compound of this invention (50 mg/kg) one hour after the initiation of the light cycle (for example, about 7 A.M.) for 18 days. Body weights are measured daily throughout the study. On
25 day 14 mice are maintained in individual metabolic chambers for indirect calorimetry assessment of energy expenditure and fuel utilization. On day 18 mice are again subjected to DEXA scanning for post treatment measurement of body composition.

The results of p.o. dosing of compound for 18 days on body weight, fat mass, and lean mass are evaluated and
30 suggest which compounds of this invention can be

especially useful for maintaining desirable weight and/or promoting desired lean to fat mass.

Indirect calorimetry measurements revealing a significant reduction in respiratory quotient (RQ) in
5 treated animals during the dark cycle [0.864 ± 0.013 (Control) vs. 0.803 ± 0.007 (Treated); $p < 0.001$] is indicative of an increased utilization of fat during the animals' active (dark) cycle and can be used to select especially desired compounds of this invention.
10 Additionally, treated animals displaying significantly higher rates of energy expenditure than control animals suggest such compounds of this invention can be especially desired.

15 Male KK/A^y Mice

Male KK/A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty-two weeks of age the
20 mice are randomly assigned to vehicle control and treated groups based on plasma glucose levels. Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (30 mg/kg) one hour after the initiation of the light cycle (7 A.M.) for 14 days.
25 Plasma glucose, triglyceride, and insulin levels are assessed on day 14.

The results of p.o. dosing of compound for 14 days on plasma glucose, triglycerides, and insulin are evaluated to identify compounds of this invention which
30 may be especially desired.

Method to Elucidate the LDL-cholesterol Total-cholesterol and Triglyceride Lowering Effect

Male Syrian hamsters (Harlan Sprague Dawley) weighing 80-120 g are placed on a high-fat cholesterol-rich diet for two to three weeks prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Under these conditions, hamsters become hypercholesterolemic showing plasma cholesterol levels between 180-280 mg/dl. (Hamsters fed with normal chow have a total plasma cholesterol level between 100-150 mg/dl.) Hamsters with high plasma cholesterol (180 mg/dl and above) are randomized into treatment groups based on their total cholesterol level using the GroupOptimizeV211.xls program.

A Compound of this invention is dissolved in an aqueous vehicle (containing CMC with Tween 80) such that each hamster received once a day approx. 1 ml of the solution by gavage at doses 3 and 30 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) is given as a known alpha-agonist control at a dose of 200 mg/kg, and the blank control is vehicle alone. Dosing is performed daily in the early morning for 14 days.

Quantification of Plasma Lipids :

On the last day of the test, hamsters are bled (400 ul) from the suborbital sinus while under isoflurane anesthesia 2 h after dosing. Blood samples are collected into heparinized microfuge tubes chilled in ice bath. Plasma samples are separated from the blood cells by brief centrifugation. Total cholesterol and triglycerides are determined by means of enzymatic assays carried out

automatically in the Monarch equipment (Instrumentation Laboratory) following the manufacturer's procedure. Plasma lipoproteins (VLDL, LDL and HDL) are resolved by injecting 25 ul of the pooled plasma samples into an FPLC system eluted with phosphate buffered saline at 0.5 ml/min through a Superose 6 HR 10/30 column (Pharmacia) maintained room temp. Detection and characterization of the isolated plasma lipids are accomplished by postcolumn incubation of the effluent with a Cholesterol/HP reagent (for example, Roche Lab System; infused at 0.12 ml/min) in a knitted reaction coil maintained at 37°C. The intensity of the color formed is proportional to the cholesterol concentration and is measured photometrically at 505 nm.

The effect of administration of a Compound of this invention for 14 days is studied for the percent reduction in LDL level with reference to the vehicle group. Especially desired compounds are markedly more potent than fenofibrate in LDL-lowering efficacy. Compounds of this invention that decrease LDL greater than or equal to 30% (thirty percent) compared to vehicle can be especially desired.

The total-cholesterol and triglyceride lowering effects of a Compound of this invention is also studied. The data for reduction in total cholesterol and triglyceride levels after treatment with a compound of this invention for 14 days is compared to the vehicle to suggest compounds that can be particularly desired. The known control fenofibrate did not show significant efficacy under the same experimental conditions.

Method to Elucidate the Fibrinogen-Lowering Effect of
PPAR Modulators

Zucker Fatty Rat Model:

- 5 The life phase of the study on fibrinogen-lowering effect of compounds of this invention is part of the life phase procedures for the antidiabetic studies of the same compounds. On the last (14th) day of the treatment period, with the animals placed under surgical
10 anesthesia, ~ 3ml of blood is collected, by cardiac puncture, into a syringe containing citrate buffer. The blood sample is chilled and centrifuged at 4°C to isolate the plasma that is stored at -70 °C prior to fibrinogen assay.

15 **Quantification of Rat Plasma Fibrinogen:**

- Rat plasma fibrinogen levels are quantified by using a commercial assay system consists of a coagulation instrument following the manufacturer's protocol. In
20 essence, 100 ul of plasma is sampled from each specimen and a 1/20 dilution is prepared with buffer. The diluted plasma is incubated at 37°C for 240 seconds. Fifty microliters of clotting reagent thrombin solution (provided by the instrument's manufacturer in a standard
25 concentration) is then added. The instrument monitors the clotting time, a function of fibrinogen concentration quantified with reference to standard samples. Compounds that lower fibrinogen level greater than vehicle can be especially desired.

- 30 Cholesterol and triglyceride lowering effects of compounds of this invention are also studied in Zucker rats.

Method to Elucidate the Anti-body Weight Gain and Anti-appetite Effects of Compounds of this invention

Fourteen-Day Study in Zucker Fatty Rat¹ or ZDF Rat²

5 Models :

Male Zucker Fatty rats, non-diabetic (Charles River Laboratories, Wilmington, MA) or male ZDF rats (Genetic Models, Inc, Indianapolis, IN) of comparable age and
10 weight are acclimated for 1 week prior to treatment. Rats are on normal chow and water is provided ad libitum throughout the course of the experiment.

Compounds of this invention are dissolved in an aqueous
15 vehicle such that each rat received once a day approximately 1 ml of the solution by garvage at doses 0.1, 0.3, 1 and 3 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) a known alpha-agonist given at doses of 300 mg/kg, as well
20 as the vehicle are controls. Dosing is performed daily in the early morning for 14 days. Over the course of the experiment, body weight and food consumption are monitored.

Using this assay, compounds of this invention are
25 identified to determine which can be associated with a significant weight reduction.

Method to elucidate the activation of the PPAR delta receptor *in vivo*

This method is particularly useful for measuring the
in vivo PPARdelta receptor activation of compounds of
30 this invention that are determined to possess significant in vitro activity for that receptor isoform over the PPAR gamma isoform.

Male PPARa null mice (129s4 SvJae-PPARa<tmlGonz> mice; Jackson Laboratories) of 8-9 weeks of age are maintained on Purina 5001 chow with water ad libitum for at least one week prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Using the GroupOptimizeV211.xls program, mice are randomized into treatment groups of five animals each based on their body weight.

Compounds of this invention are suspended in an aqueous vehicle of 1% (w/v) carboxymethylcellulose and 0.25% Tween 80 such that each mouse receives once a day approx. 0.2 ml of the solution by gavage at doses ranging from 0.2 to 20 mg/kg body weight. A control group of mice is included in each experiment whereby they are dosed in parallel with vehicle alone. Dosing is performed daily in the early morning for 7 days.

On the last day of dosing, mice are euthanized by CO2 asphyxiation 3 hours after the final dose. Blood samples are collected by heart draw into EDTA-containing microfuge tubes and chilled on ice. Liver samples are collected by necropsy and are flash-frozen in liquid nitrogen and stored at -80 degrees Celsius. For RNA isolation from liver, five to ten mg of frozen liver is placed in 700 µl of 1x Nucleic Acid Lysis Solution (Applied Biosystems Inc., Foster City, CA) and homogenized using a hand-held tissue macerator (Biospec Products Inc., Bartlesville, OK). The homogenate is filtered through an ABI Tissue pre-filter (Applied Biosystems Inc., Foster City, CA) and collected in a deep well plate on an ABI 6100 Nucleic Acid prep station (Applied Biosystems Inc., Foster City, CA). The filtered

homogenate is then loaded onto an RNA isolation plate and the RNA Tissue-Filter-DNA method is run on the ABI 6100. The isolated RNA is eluted in 150 µl of RNase free water. For quality assessment, 9 µl of the isolated RNA solution
5 is loaded onto a 1% TBE agarose gel, and the RNA is visualized by ethidium bromide fluorescence.

Complementary DNA (cDNA) is synthesized using the ABI High Capacity Archive Kit (Applied Biosystems Inc., Foster City, CA). Briefly, a 2x reverse transcriptase
10 Master Mix is prepared according to the manufacturer's protocol for the appropriate number of samples (RT Buffer, dNTP, Random Primers, MultiScribe RT (50U/µl), RNase free water). For each reaction, 50 µl of 2x RT Master Mix is added to 50 µl of isolated RNA in a PCR
15 tube that is incubated in a thermocycler (25°C for 10 minutes followed by 37°C for 2 hours). The resultant cDNA preparation is diluted 1:100 in dH2O for analysis by real-time PCR. Also, a standard curve of cDNA is diluted 1:20, 1:100, 1:400, 1:2000, 1:10,000 for use in final
20 quantitation.

A real-time PCR Master Mix for mouse Cyp4A1 gene expression is mixed to contain:

- 1X Taqman Universal PCR Master Mix (Applied Biosystems Inc., Foster City, CA)
25
- 6 micromolar final concentration Forward primer; Qiagen/Operon Technologies, Alameda, CA)
- 6 micromolar final concentration Reverse
30 primer (Qiagen/Operon Technologies, Alameda, CA)

- 0.15 micromolar final concentration Probe (5' 6-FAM and 3' Tamra-Q; Qiagen/Operon Technologies, Alameda, CA)
- RNase free water to 10 microliters

5

A real-time PCR Master Mix for the 18S ribosomal RNA control gene expression is mixed to contain

10

- 1X Taqman Universal PCR Master Mix (Applied Biosystems Inc., Foster City, CA)
- 0.34 micromolar Probe/Primer TaqMan® Ribosomal RNA Control Reagents #4308329 Applied Biosystems Inc., Foster City, CA)
- RNase free water to 10 microliters

15

For the real-time PCR analysis, 6 ul of the respective Master Mix solution (either Cyp4A1 or 18S) and 4 ul either of diluted cDNA or of Standard Curve samples is added to individual wells of a 384-well plate (n = 2 for Standards; n = 4 for unknowns). Reactions are performed using the ABI 7900 HT standard universal RT-PCR cycling protocol. Data are analyzed using SDS 2.1 (Applied Biosystems Inc., Foster City, CA). Average quantity and standard deviation are calculated automatically for each individual sample, according to the standard curve values. Using Microsoft Excel 2000, mean values for each group of five individual mice is calculated. The mean value of each compound-treated

20

25

group is divided by the mean value of the vehicle-treated group. The fold induction over the vehicle group is determined by assigning the vehicle group to the value of 1.0, and the fold change of the mean value for each group is expressed as fold-induction versus vehicle (1.0). Data are plotted using Jandel SigmaPlot 8.0.

Monkey studies

Efficacy Studies

Compounds of the invention may be examined in a dyslipidemic rhesus monkey model. After an oral dose-escalation study for 28 days in obese, non-diabetic rhesus monkeys a determination of HDL-c elevation is made with each dose and compared with pretreatment levels. LDL cholesterol is also determined with each dose. C-reactive protein levels are measured and compared to pretreatment levels.

Compound of Formula 1 may be shown to elevate plasma HDL-cholesterol levels in an African Green Monkey model in a manner similar to that described above in rhesus monkeys.

Two groups of monkeys are placed in a dose-escalating study that consists of one week of baseline measurements, 9 weeks of treatments (vehicle, Compound of Formula I), and four weeks of washout. During baseline, monkeys in all three groups are administered vehicle once daily for

seven days. Test compound of Formula I, is administered in vehicle once daily for three weeks, then at a greater concentration (double the dose may be desired) once daily for three weeks, and then a still greater concentration (double the most recent dose may be desired) once daily for three weeks. At the completion of treatment, monkeys in both groups are administered vehicle once daily and monitored for an additional six weeks.

Animals are fasted overnight and then sedated for body weight measurements and blood collection at weeks 1 (vehicle), 2, 3, 4, 6, 7, 9, 10, 12, and 14 of the study.

Parameters to measured, for example:

Body weight
Total plasma cholesterol
HDL
LDL
Triglycerides
Insulin
Glucose
PK parameters at week 4, 7, and 10 (plasma drug concentration at last week of each dose)
ApoAI
ApoAII
ApoB
ApoCIII
Liver enzymes (SGPT, SGOT, \square GT)
Complete blood count

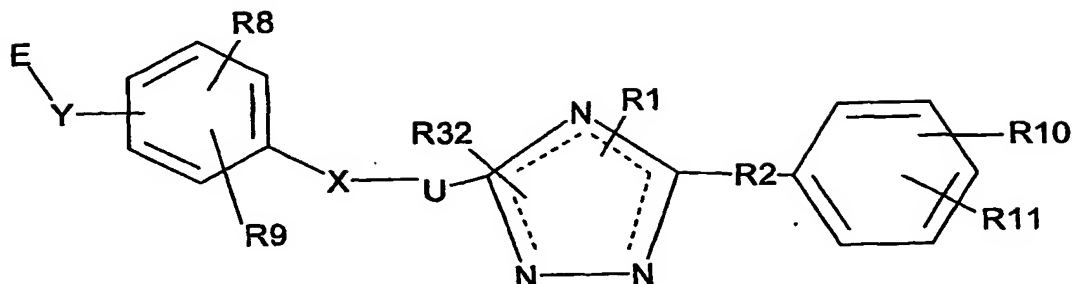
Additionally, other measures may be made, as appropriate, and consistent with the stated study design.

EQUIVALENTS:

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

1. A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C₃-C₆ cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

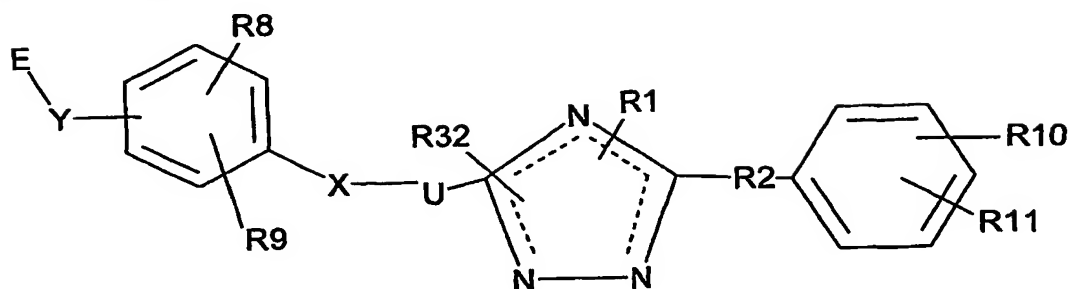
(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀-4-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14,

- 5 OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19,
NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and
S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17,
R18, R19, R20, R21, R22, R23, R24 and R25 are
each independently selected from the group
consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R2 is selected from the group consisting of C₀-
C₈ alkyl and C₁₋₄-heteroalkyl;
- 10 (d) X is selected from the group consisting of a
single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon
atom of the aliphatic linker is optionally
replaced with O, NH or S, and wherein such
aliphatic linker is optionally substituted with
15 from one to four substituents each
independently selected from R30;
- (f) Y is selected from the group consisting of C,
NH, and a single bond;
- 20 (g) E is C(R3)(R4)A or A and wherein
(i) A is selected from the group consisting
of carboxyl, tetrazole, C₁-C₆ alkyl nitrile,
carboxamide, sulfonamide and
acylsulfonamide; wherein sulfonamide,
acylsulfonamide and tetrazole are each
25 optionally substituted with from one to two
groups independently selected from R⁷;
- (ii) each R⁷ is independently selected from
the group consisting of hydrogen, C₁-C₆
haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;

- (iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C₃-C₆

- 5 cycloalkylaryl-C₀-2-alkyl, aryloxy, C(O)R₁₃',
COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂,
NR₁₈'C(O)R₁₉', NR₂₀'SO₂R₂₁', SR₂₂', S(O)R₂₃',
S(O)₂R₂₄', and S(O)₂N(R₂₅')₂; and wherein aryl-
C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-
C₀-4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl
are each optionally substituted with from one
to three independently selected from R₂₈; and
10 wherein R₁₀ and R₁₁ optionally combine to form
a 5 to 6 membered fused bicyclic ring with the
phenyl to which they are bound;
- (k) R₁₂', R₁₂'', R₁₃', R₁₄', R₁₅', R₁₆', R₁₇',
R₁₈', R₁₉', R₂₀', R₂₁', R₂₂', R₂₃', R₂₄', and
R₂₅' are each independently selected from the
15 group consisting of hydrogen, C₁-C₆ alkyl and
aryl;
- (l) R₃₀ is selected from the group consisting of
C₁-C₆ alkyl, aryl-C₀-4-alkyl, aryl- C₁-4-
heteroalkyl, heteroaryl-C₀-4-alkyl, and C₃-C₆
20 cycloalkylaryl-C₀-2-alkyl, and wherein C₁-C₆
alkyl, aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl,
heteroaryl-C₀-4-alkyl, and C₃-C₆
cycloalkylaryl-C₀-2-alkyl are each optionally
substituted with from one to three substituents
25 each independently selected from R₃₁;
- (m) R₃₂ is selected from the group consisting of a
bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆
haloalkyl, and C₁-C₆ alkyloxy; and
- (n) ---- is optionally a bond to form a double bond
30 at the indicated position.

2. A compound of the Formula II:



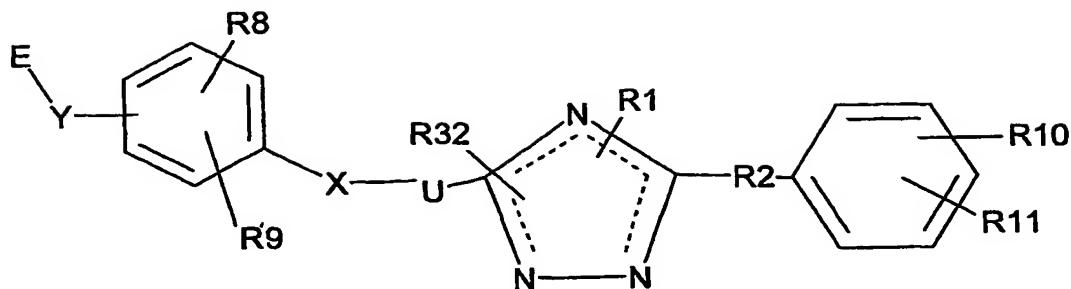
and stereoisomers, pharmaceutically acceptable
5 salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of
hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-
4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-
4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl,
10 and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-
C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-
C₀-4-alkyl, C₃-C₆ cycloalkylaryl-C₀-2-alkyl are
each optionally substituted with from one to
15 three substituents independently selected from
R1';
- (b) R1', R26, R27, R28 and R31 are each
independently selected from the group
consisting of hydrogen, hydroxy, cyano, nitro,
20 halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12, C₁-C₆
alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-
C₇ cycloalkyl, aryloxy, aryl-C₀-4-alkyl,
heteroaryl, heterocycloalkyl, C(O)R13, COOR14,
OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19,
25 NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and

- S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 5 (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁-₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- 10 (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R30;
- 15 (f) Y is selected from the group consisting of C, O, S, NH and a single bond;
- (g) E is C(R3)(R4)A or A and wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
- 20 (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- 25 (iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy;
- 30 and

- (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- 5
- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- 10
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of
- 15
- hydrogen and C₁-C₄ alkyl;
- 20
- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkylenyl, C₁-C₆ alkyl-COOR12'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C₃-C₆ cycloalkylaryl-C₀-2-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23',
- 25
- 30

- 5 S(O)₂R_{24'}, and S(O)₂N(R_{25'})₂; and wherein aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C3-C6 cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- 10 (k) R_{12'}, R_{12''}, R_{13'}, R_{14'}, R_{15'}, R_{16'}, R_{17'}, R_{18'}, R_{19'}, R_{20'}, R_{21'}, R_{22'}, R_{23'}, R_{24'}, and R_{25'} are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 15 (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C3-C6 cycloalkylaryl-C₀-2-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C3-C6 cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;
- 20 (m) R₃₂ is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and
- 25 (n) ---- is optionally a bond to form a double bond at the indicated position.
3. A compound of the Formula III:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

5

(a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-₄-alkyl, aryl-C₁-₄-heteroalkyl, heteroaryl-C₀-₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀-₂-alkyl, and, wherein C₁-C₈ alkyl, C₁-C₈ alkenyl, aryl-C₀-₄-alkyl, aryl-C₁-₄-heteroalkyl, heteroaryl-C₀-₄-alkyl, C₃-C₆ cycloalkylaryl-C₀-₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

15

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀-₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19, NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17,

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25

- R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- 5 (c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁-4-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- 10 (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- 15 (f) Y is selected from the group consisting of O, S, NH, C, and a single bond;
- (g) E is C(R3)(R4)A; wherein
- (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each
- 20 optionally substituted with from one to two groups independently selected from R⁷;
- (ii) each R⁷ is independently selected from
- 25 the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R3 is selected from the group consisting of C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- 30 (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy,

C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R₂₆;

with the proviso that when Y is O then R₄ is selected from the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R₂₆;

(h) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;

(i) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

(j) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆

- alkylenyl, C₁-C₆ alkyl-COOR₁₂'', C₀-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C₃-C₆ cycloalkylaryl-C₀-2-alkyl, aryloxy, C(O)R₁₃', COOR₁₄', OC(O)R₁₅', OS(O)₂R₁₆', N(R₁₇')₂, NR₁₈'C(O)R₁₉', NR₂₀'SO₂R₂₁', SR₂₂', S(O)R₂₃', S(O)₂R₂₄', and S(O)₂N(R₂₅')₂; and wherein aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three independently selected from R₂₈; and wherein R₁₀ and R₁₁ optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R₁₂', R₁₂'', R₁₃', R₁₄', R₁₅', R₁₆', R₁₇', R₁₈', R₁₉', R₂₀', R₂₁', R₂₂', R₂₃', R₂₄', and R₂₅' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀-4-alkyl, aryl- C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, and C₃-C₆ cycloalkylaryl-C₀-2-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁;

(m) R32 is selected from the group consisting of a bond, hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and C₁-C₆ alkyloxo; and

(n) ---- is optionally a bond to form a double bond at the indicated position.

5

4. A compound as claimed by any one of Claims 1 through 3 wherein X is -O-.

5. A compound as claimed by any one of Claims 1 through 3 wherein X is -S-.

10

6. A compound as claimed by any one of Claims 2 through 5 wherein Y is O.

7. A compound as claimed by any one of Claims 2 through 5 wherein Y is C.

15

8. A compound as claimed by any one of Claims 1 through 5 wherein Y is S.

9. A compound as claimed by any one of Claims 1 through 8 wherein ---- is a bond to form a double bond at the designated location on Formula I.

20

10. A compound as claimed by any one of Claims 1 through 8 wherein two of "----" in the five membered ring are each a bond to form double bonds at the designated locations.

11. A compound as claimed by any one of Claims 1 through 10 wherein E is C(R3)(R4)A.

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12. A compound as claimed by any one of Claims 1 through 11 wherein A is COOH.

13. A compound as claimed by any one of Claims 1 through 12 wherein R10 is haloalkyl.

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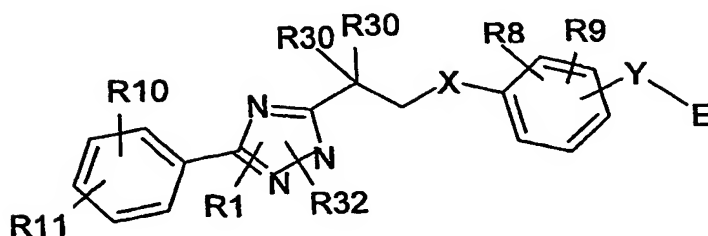
14. A compound as claimed by any one of Claims 1 through 12 wherein R10 is CF₃.

15. A compound as claimed by any one of Claims 1 through 12 wherein R10 is haloalkyloxy.
- 5 16. A compound as claimed by any one of Claims 1 through 12 wherein R10 and R11 are each independently selected from the group consisting of hydrogen, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂'', C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkyloxy.
- 10 17. A compound as claimed by any one of Claims 1 through 12 wherein R10 is selected from the group consisting of C₃-C₇ cycloalkyl, aryl-C₀-4-alkyl, aryl-C₁-4-heteroalkyl, heteroaryl-C₀-4-alkyl, C₃-C₆ cycloalkylaryl-C₀-2-alkyl, and aryloxy.
- 15 18. A compound as claimed by any one of Claims 1 through 17 wherein R1 is optionally substituted C₂-C₃ arylalkyl.
- 20 19. A compound as claimed by any one of Claims 1 through 17, wherein R8 and R9 are each independently selected from the group consisting of hydrogen and C₁-C₃ alkyl.
- 25 20. A compound as claimed by any one of Claims 1 through 17 and 19 wherein R1, R2, R3, and R4 are each independently selected from the group consisting of C₁-C₂ alkyl.
- 30 21. A compound as claimed by any one of Claims 1 through Claim 17 and 19 wherein R1, R3, and R4 are each independently selected from the group consisting of hydrogen and C₁-C₂ alkyl.

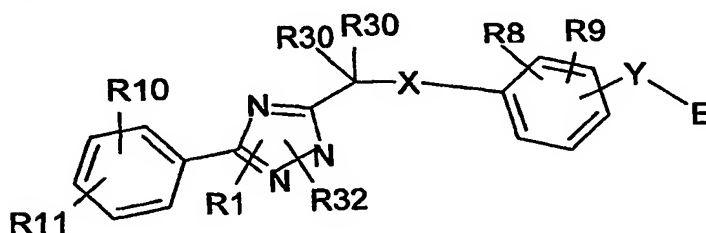
22. A compound as claimed by any one of Claims 1 through 17 wherein R2 is a bond.
23. A compound as claimed by any one of Claims 1 through 19 wherein R2 is selected from the group consisting of C₀-C₁ alkyl;
- 5 24. A compound as claimed by any one of Claims 1 through 23 wherein U is C₁-C₃ alkyl.
25. A compound as claimed by any one of Claims 1 through 24 wherein U is saturated.
- 10 26. A compound as claimed by any one of Claims 1 through 25 wherein U is substituted with C₁-C₃ alkyl.
27. A compound as claimed by any one of Claims 24, 25 and 26 wherein one carbon of the aliphatic linker is replaced with an O.
- 15 28. A compound as claimed by any one of Claims 1 through 26 wherein U is an aliphatic linker having one carbon replaced by S.
29. A compound as claimed by any one of Claims 1 through 28 wherein the aliphatic linker is substituted with from one to three substituents each independently selected from R30.
- 20 30. A compound as claimed by Claim 29 wherein the aliphatic linker is substituted with from one to two substituents each independently selected from R30.
- 25 31. A compound as claimed by any one of Claims 1 through 30 wherein each R30 is independently selected from the group consisting of C₁-C₆ alkyl.
- 30

32. A compound as claimed by any one of Claims 1 through 31 wherein each R30 is independently selected from the group consisting of C2-C3 alkyl.
- 5 33. A compound as claimed by any one of Claims 1 through 30 wherein R30 is independently selected from the group consisting of aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6
- 10 cycloalkylaryl-C₀₋₂-alkyl.
34. A compound as claimed by any one of Claims 1 through 33 wherein two of "----" each form a double bond in the five membered ring at the designated position.
- 15 35. A compound as claimed by Claim 34 wherein Y is O and E is -CH₂COOH.
36. A compound as claimed by any one of Claims 1 through 35 wherein U is substituted with methyl.
- 20 37. A compound as claimed by any one of Claims 1 through 36 wherein U is methylene.
38. A compound as claimed by any one of Claims 1 through 12, Claims 18 through 37 wherein R10 and R11 combine to form a fused 6
- 25 membered ring.
39. A compound as claimed by any one of Claims 1 through 10, one of Claims 17 through 25, or one of Claims 27 through 36 represented

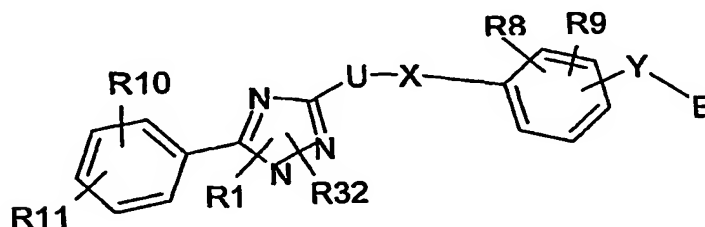
by the following Structural Formula II:



40. A compound as claimed by any one of Claims 1 through 10, or one of Claims 17 through 37 represented by the following Structural Formula III:

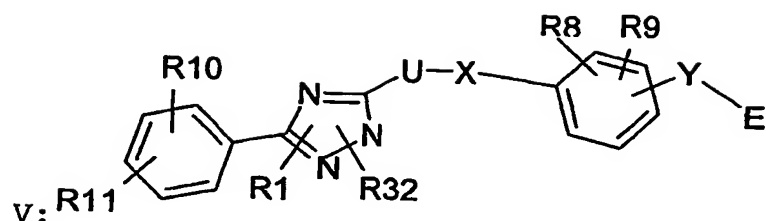


41. A compound as claimed by any one of Claims 1 through 10, or one of Claims 17 through 37 represented by the following Structural Formula IV:

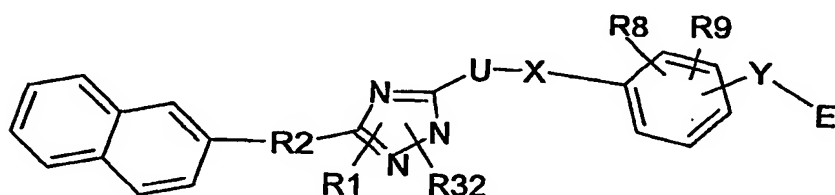


42. A compound as claimed by any one of Claims 1 through 10 or one of Claims 17 through 37 represented by the following Structural

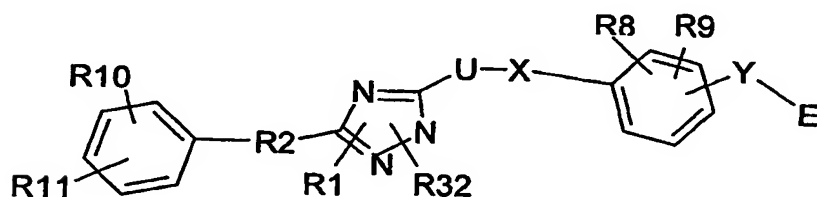
Formula



43. A compound as claimed by any one of Claims 1 through 10, Claims 17 through 37 represented by the following Structural Formula:



44. A compound as claimed by any one of Claims 1 through 10, Claims 17 through 37 represented by the following Structural Formula:



45. A compound as claimed by any one of Claims 1 through 44 wherein X and Y are substituted at a 1,4-position, such that X and Y are para substituted to one another.
46. A compound as claimed by any of of Claims 1 through 45 wherein X and Y are substituted at a 1,3-position, such that X and Y are meta substituted to one another.

47. A compound as claimed by any one of Claims 1 through 3 wherein the compound is selected from the group consisting of

48. A compound as claimed by any one of Claims 1 through 3 which is a compound of Formula I selected from the group consisting of.

49. A compound as claimed by any one of Claims 1 through 3 which is 2-Methyl-2-{4-[3-(5-naphthalen-2-ylmethyl-2H-[1,2,4]triazol-3-yl)-phenoxy]propionic acid.

50. A compound as claimed by any one of Claims 1 through 49 that is the S conformation.

51. A compound as claimed by any one of Claims 1 through 49 that is the R conformation.

52. A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by any one of Claims 1 through 51 together with a pharmaceutically acceptable carrier or diluent.

53. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1 through 51.

54. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 51.

55. A method of treating metabolic disorder in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 51.
56. A method of Claim 55 wherein the mammal in need thereof is diagnosed as suffering from metabolic disorder.
57. A method of selectively modulating a PPAR delta receptor comprising administering a compound as claimed by any one of Claims 1 through 51 to a mammal in need thereof.
58. The manufacture of a medicament for use in the treatment and/or prevention of a condition mediated by nuclear receptors, in particular by a peroxisome proliferator activated receptor, wherein the compound is a compound as claimed by any one of Claims 1 through 51.
59. A method of treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound of Claims 1 through 51.
60. A compound as Claimed by any one of Claims 1 through 51 for use as a pharmaceutical.
61. A method for treating or preventing the progression of cardiovascular disease in a mammal in need thereof comprising administering a therapeutically effective

amount of a compound as Claimed by any one of Claims 1 through 51.

62. A method as claimed by Claim 61 wherein the mammal is diagnosed as being in need of such treatment.

63. A compound as claimed by any one of Claims 1 through 51 wherein the compound is radiolabeled.

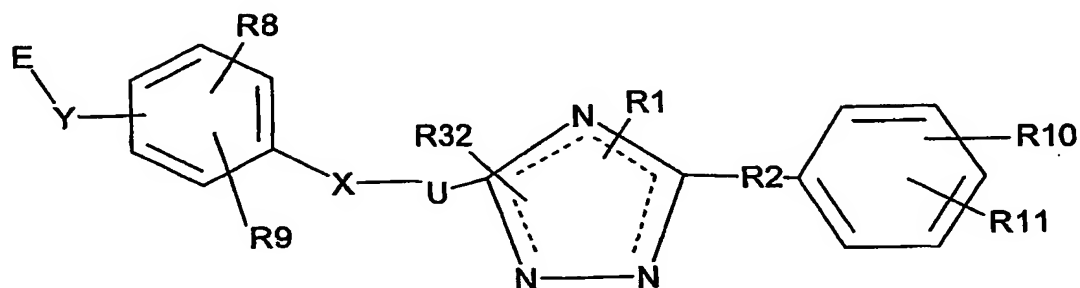
64. A compound as disclosed by any one of the Examples herein.

65. All methods disclosed herein of preparing the compounds represented by Structural Formula I.

ABSTRACT

The present invention is directed to compounds represented by the following structural formula, Formula

5 I:



wherein:

- 10 (a) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (b) U is an aliphatic linker;
- (c) Y is selected from the group consisting of O, C, S, NH and a single bond;
- 15 (d) E is C(R3)(R4)A or A and wherein
- (e) (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkynitrile, carboxamide, sulfonamide and acylsulfonamide.

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